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Review Article

Sleep-related disturbances among adolescents with cancer: a systematic review

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ABSTRACT

The purpose of this systematic review was to examine the evidence for sleep-related disturbances among adolescents with cancer, particularly the types of disturbances reported, using single and mixed paediatric oncology samples. *Methods:* Electronic searches of Medline, PubMed, and the Cochrane Database of Systematic Reviews since inception to September 2013 were conducted to identify all relevant studies. Search terms included sleep, a second term including adolescent, juvenile, youth, child, or childhood, and a third term including cancer, leukaemia, or brain tumour. A total of 41 articles met inclusion criteria and were included in the review. Of these, 32 included patients with leukaemia and 21 included patients with brain tumours. Sleep-related disturbances included difficulty initiating sleep, fragmented sleep, disordered breathing, parasomnias, napping, daytime sleepiness/fatigue, and unspecified disturbances. Adolescents with cancer experience many problems related to sleep. Given the increase in survival rates of the youth diagnosed with leukaemia or brain tumours, symptom management is an essential area of research in order to continue improving quality of life.

1. Introduction

While cancer is exceeded only by accidents as a leading cause of death among the youth, mortality rates have declined by 68% over the past four decades [1]. For adolescents, the 5-year relative survival rate across malignant cancer diagnoses has increased from 68.7% to 84.5% [2]. Advances in medical treatment and support care have led to the reconsideration of cancer from being an inevitably life-ending disease to a life-changing chronic illness. The long-term implications of being a survivor of childhood cancer have received increasing attention, as has the necessity of understanding and improving the child's quality of life both during and after treatment.

The relationship between sleep and quality of life among paediatric oncology patients has been the focus of increasing attention; however, less is still currently known about the effects of cancer, its treatment, and concurrent symptoms on sleep than about other variables such as pain or family functioning [3]. Sleep is a biologically necessary state of disengagement with an unresponsiveness to the environment thought to be involved in metabolic regulation, hormone production, immune functioning, and memory consolidation [4,5]. Insufficient sleep in adolescence is associated with deficits in social skills, emotional regulation, physical coordination, and cognition, as well as a potential increase in susceptibility to chronic health conditions such as diabetes and obesity [6].

The most common cancers diagnosed in childhood and adolescence are leukaemias, brain tumours, lymphoma, sarcomas, and germ cell tumours, a distribution different from the most prevalent diagnoses among young adults or adults [7,8]. Particularly between the time period that begins just prior to puberty and ends with the societal connotation of adult status, the human body undergoes a myriad of physical, emotional, social, and cognitive changes. When cancer occurs during this period, it is likely that the disease- and symptom-related experience would be quite different from those during the earlier or later stages of life. Given this, as well as the detrimental effects of insufficient or inefficient sleep, the purpose of this systematic review was to examine the evidence for sleep-related disturbances among adolescents with cancer, particularly the types of disturbances reported, using single and mixed paediatric oncology samples.

2. Methods

Electronic searches of Medline, PubMed, and the Cochrane Database of Systematic Reviews since inception to September 2013 were conducted to identify all relevant studies. Search terms included sleep, a second term including adolescent, juvenile, youth,

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child, or childhood, and a third term including cancer, leukaemia, or brain tumour. Leukaemia and brain tumours were chosen because they are the two most frequently occurring cancers in youth and have been the focus of multiple studies. When studies included many participants with different cancer diagnoses, the author attempted to use only data specifically linked to leukaemia or a brain tumour. Given that publications do not always provide information on specific types of brain tumours, these were examined as a single category and not differentiated by type. In accordance with the World Health Organization definition, adolescents were defined as being between 10 and 19 years of age, and studies were selected in which the majority of participants were between those ages. Resultant lists from the initial database searches were screened for relevant titles; abstracts of selected titles were reviewed, and appropriate articles were examined for data on patient age range, sleep-related disturbances, and type of cancer. Reference lists and PubMed "related links" were also used to identify additional articles; no attempts were made to identify unpublished studies. Excluded articles included those that involved community-based samples, were written in a language other than English, were reviews of multiple studies or involved explicit measurement development or validation. Of primary interest were articles that simply examined the self- or other-reported sleep disorders in the population of interest.

3. Results

A total of 41 articles met inclusion criteria and were included in the review (Fig. 1). Of these, 31 included patients with leukaemia and 21 included patients with brain tumours. The articles were published between 1992 and 2013, with the majority ($n = 34$) being published after 2000. Table 1 provides an overview of the studies reviewed, including cancer diagnosis, number of identified articles, treatment and steroid status, total number of participants, and assessment measures used.

Table 2 provides information of the types of sleep-related disturbances reported. The most frequently reported disturbances were difficulty initiating sleep, fragmented sleep, disordered breathing, parasomnias, napping, excessive daytime sleepiness (EDS), fatigue, and sleep disturbance unspecified.

3.1. Difficulty Initiating Sleep

A total of seven articles reported difficulty initiating sleep; all seven included adolescents with leukaemia [9–16] and five included adolescents with a brain tumour [9–11,15,16]. Difficulty falling asleep was assessed via adolescent interview [10,14,15], actigraphy [12,13], polysomnography [11], adolescent self-report questionnaire [9], caregiver interview [15], and caregiver self-report questionnaire [16]. Inability to fall asleep was reported to be precipitated by psychological distress [10,14,16], discomfort/pain [10,11,14,15], or spending the night in the hospital [14]. No study reported whether differences existed between males and females in difficulty initiating sleep, although gender accounted for 5% of the variance in sleep quality in one study [9]. The majority of studies reported results for patients receiving treatment for leukaemia [9–15]. Strategies to aid in the onset of sleep were described in one study [11] and included sleep restriction, sleep hygiene education, medication for pain control, sedative hypnotics, and melatonin.

3.2. Fragmented sleep

A total of 17 articles reported fragmented nigh-time sleep; 14 included adolescents with leukaemia [9,12–14,16–26,41,42], and seven included adolescents with brain tumors [9,16,17,22,41,42]. Nocturnal wakings were determined by actigraphy [12,13,17–20,23–25,42], caregiver self-report questionnaires [16,20,21,26], adolescent self-report questionnaires [9,21,26], adolescent interview [14], caregiver interview [22], and polysomnography [41]. Studies reported up to 40 night wakings [18,19,24,25], and one study reported that the cumulation of such wakings totalled >85 min [17]. Actigraphy indicated more wakings than sleep diaries did, suggesting that the frequency of night-time wakings may be under-reported by subjective measures [24]. Wake after

Table 1
Characteristics of studies reporting sleep-related difficulties among adolescents with cancer.

Diagnosis	Number of Studies		
Leukaemia only	20		
Brain tumour only	9		
Both leukaemia and brain tumour	12		
Total number of studies	41		
Diagnosis (from single- and combined-sample studies)	Receiving treatment	Not receiving treatment	
Leukaemia	31 Studies	1 Study	
Brain tumour	11 Studies	10 Studies	
Diagnosis	Receiving steroids	Not receiving steroids	Steroid administration unclear
Leukaemia	8 Studies	2 Studies	22 Studies
Brain tumour	1 Study	10 Studies	10 Studies
Diagnosis (from single- and combined-sample studies)	Total sample size (N)		
Leukaemia	457		
Brain tumour	239		
Both diagnoses total sample size	696		
Diagnosis	Assessment measures used		
Leukaemia	Self-report ($n = 26$); caregiver-report ($n = 14$); actigraphy ($n = 10$); polysomnography ($n = 2$); multiple sleep latency test ($n = 1$); staff-report ($n = 1$); imaging ($n = 1$)		
Brain tumour	Self-report ($n = 12$); caregiver-report ($n = 6$); polysomnography ($n = 6$); multiple sleep latency test ($n = 4$); actigraphy ($n = 4$); imaging ($n = 1$)		

Table 2
Sleep-related disturbances among adolescents with cancer.

	Difficulty initiating sleep	Fragmented sleep	Disordered breathing	Parasomnias	Napping	Excessive daytime sleepiness	Fatigue	Sleep disturbances unspecified
Leukaemia								
Receiving treatment	7 Articles [9–15]	16 Articles [9,12–14,17–26]	2 Articles [11,27]	4 Articles [11,15,20,21]	6 Articles [13,14,19,22,23,28]	5 Articles [11,22,31–33]	21 Articles [10,12,14,18,19,21, 23–26,28–31,34–40]	
Off Treatment	1 Article [16]	1 Article [16]						
Brain tumour								
Receiving treatment	3 Articles [9,10,15]	3 Articles [9,17,22]		1 Article [15]	1 Article [22]	2 Articles [22,31]	6 Articles [10,31,36,37,39,40]	
Off treatment	2 Articles [11,16]	4 Articles [16,41,42]	5 Articles [11,43–46]	1 Article [11]	3 Articles [42,44,47]	8 Articles [11,16,41,43–45,47,48]		1 Article [49]

sleep onset (WASO) refers to the amount of time spent awake after sleep has been initiated but before final awakening. Increased WASO as measured by actigraphy was reported [12,13,17–19], and males demonstrated increased WASO across treatment times compared to females [19]. Another study similarly reported that males experienced nocturnal awakenings than females [23]. Increased WASO and nocturnal wakings were associated with the pro-inflammatory cytokine tumour necrosis factor (TNF) in patients with acute lymphoblastic leukaemia [13].

Waking up throughout the night was reportedly caused by parasomnias [20–22], being hungry [20–22], needing to use the bathroom [20–22], fear/anxiety [14,21,22], being thirsty [20,22], nausea or vomiting [21,22], and pain [20,22]. Hospitalisation was associated with increased night-time wakings [14,18,22,25,26] and for some, wakings did not decrease as time in the hospital increased [18]. Having a parent or guardian sleep overnight in the hospital room, however, was associated with a decrease in night-time wakings [18]. The onset of frequent wakings varied, with some studies reporting that they were not occurring prior to cancer diagnosis [21] or chemotherapy [20] and were related to steroid administration [21–23]; however, some parents also indicated that the number of wakings per night did not seem to have increased for their child following diagnosis and/or treatment initiation [20–22,27]. Adolescents were receiving treatment for leukaemia in a majority of studies [9,12–14,17–26]. Treatment to facilitate reinitiation of sleep was not described in any of the aforementioned studies.

3.3. Disordered breathing

A total of six articles reported disordered breathing; two included adolescents with leukaemia [11,27] and five included adolescents with a brain tumour [11,43–46]. Breathing disorders included central sleep apnoea [11,27,43,45], obstructive sleep apnoea [11,43–45] or apnoea unspecified [46] and were identified via polysomnography [11,43–45], adolescent self-report [46], and caregiver report [27]. Obstructive sleep apnoea was noted to occur with obesity and increased daytime sleepiness [11,43–45], although the directionality of the relationship(s) was unclear. Among adolescents with brain tumours, tumour location was reported in the hypothalamic area [11,43–45] thalamus [11,45], pituitary region [44], posterior fossa [45], and brainstem [11,45]. Breathing-related treatment included behavioural counselling [11], tracheotomy with and without a ventilator [11], bi-level positive airway control [11,27], continuous positive airway pressure [11,43,44], and medication (sedative hypnotics, stimulants, anticonvulsants, and antidepressants) [11]. No differences in the incidence of disordered breathing between males and females were reported. In the majority of studies, adolescents had previously been treated for a brain tumour and were not currently receiving treatment [11,43–46].

3.4. Parasomnias

A total of four articles reported parasomnias; all four included adolescents with leukaemia [11,15,20,21], and two included adolescents with a brain tumour [11,15]. Parasomnias included bedwetting [20], teeth grinding [20], nightmares [15,20,21], sleep walking [20], sleep eating [11], sleep talking [20], sleep-related seizures [11], and confusional arousals [11]. Parasomnias were identified by caregiver interview [11,15], adolescent interview [21], caregiver-completed Child Sleep Assessment [20], adolescent-completed Children's Sleep Habits Questionnaire [21], and polysomnography [11]. Some of the parasomnias were reported to have begun after the cancer diagnosis [11], but others were present prior to diagnosis [20]. No study directly examined the content of the nightmares, although one quoted a parent as saying their child would awaken crying and talking about fears of dying [21]. Overall, it appeared that when parasomnias were reported, they occurred in a small percentage of study participants, the majority of whom were receiving treatment for leukaemia [11,15,20,21]. Differences in frequency and intensity of parasomnias between males and females were not examined. Treatment of parasomnias included anticonvulsants [11] and sleep hygiene education [11].

3.5. Napping

A total of nine articles reported napping; six included adolescents with leukaemia [13,14,19,22,23,28], and four included adolescents with a brain tumour [22,42,44,47]. Naps were assessed via actigraphy [13,19,23,42,47], polysomnography [44,47], interviews with adolescents [14,28] and interviews with caregivers [22]. Caregiver reports indicated that adolescents receiving treatment were more likely to nap during the day compared with healthy controls [22]. Nap duration among patients with acute lymphoblastic leukaemia having the proinflammatory cytokine interleukin-6 (IL-6) promoter (−174G > C) allele was significantly shorter than among patients with other polymorphisms [13]. Based on actigraphy, females demonstrated increased frequency and duration of naps compared to males, even after controlling for age, treatment, and leukaemia risk group [19]. While the majority of adolescents in remission reported less disruption in daily functioning as time from treatment increased, difficulty making it through the day without at least one nap persisted among some survivors for 5 or more years for leukaemia [28]. Napping was also reported as a strategy to decrease fatigue [14]. Patients who had undergone resection of hypothalamic/pituitary tumours reported frequent napping and demonstrated significantly decreased time to fall asleep during multiple sleep latency testing (MSLT) compared to controls [44]. Being diagnosed with a brain tumour led to the resumption of daytime napping among adolescents who had previously discontinued napping during early childhood [42,47]. The majority of patients who napped were those receiving

treatment for leukaemia [13,14,19,22,23,25]. No study reported results of interventions addressing napping directly, but in one study of patients treated for a brain tumour, daytime napping was reported to be a symptom of EDS and was effectively controlled with stimulant medication [47].

3.6. Excessive daytime sleepiness

A total of 12 articles reported EDS; five included adolescents with leukaemia [11,22,31–33] and 10 included adolescents with a brain tumour [11,16,22,31,41,43–45,47,48]. In five studies, EDS was determined using objective measures such as polysomnography with MSLT [11,41,44,45,47], sleep onset latency as measured by polysomnography without MSLT [43,47], and actigraphy indicating inappropriate daytime napping or daytime sleep >30 min per day [11,47]. EDS was defined by report in three studies [11,22,31,48], including caregiver-reported history of adolescent frequently falling asleep during routine activities of daily living [11,22] or self-reported endorsement of drowsiness on the Memorial Symptom Assessment Scale for 10–18-year olds [31] or a version of the Epworth Sleepiness Scale [16,48]. In one study, EDS was defined based on a combination of self/caregiver-report and clinical presentation of symptoms [32]. Caregivers reported that daytime sleepiness affected their child's ability to exercise, complete homework, watch television, use a computer, stay awake both during school and on the bus ride home, and engage in social activities [11,22]. Somnolence syndrome (mild to EDS, fever, anorexia, nausea, emesis, difficulty swallowing and, cerebellar ataxia) was reported for 13 patients who received prophylactic cranial irradiation for acute lymphoblastic leukaemia [32], as well as an adolescent treated for chronic myelogneous leukaemia with a bone marrow transplant [33]. Females may have experienced greater functional limitations related to EDS [22]. In one study that assessed gender differences in daytime sleepiness, no significant differences were found [16]; however, another study showed that females reported the highest frequency of problems related to EDS and were most often in the consolidation phase of treatment for leukaemia [29]. The majority of studies reported EDS in patients who had previously received treatment for a brain tumour [11,41,43–45,47,48], located in the hypothalamic [11,43–45,47,48], thalamic [11], basal forebrain [41] or brainstem regions [11,45]. These regions are known to play an important role in regulating sleep [47]. While an association between daytime sleepiness and tumour location was not always reported to exist [16], one study concluded that when the hypothalamic/pituitary region of the brain was damaged, patients developed EDS, regardless of whether the damage was related to the tumour, surgery, hydrocephalus, or radiation [47]. Treatment of EDS included stimulant medication [11,47], growth hormone administration [44], and scheduled naps [47].

3.7. Fatigue

A total of 21 articles reported fatigue; all 21 included adolescents with leukaemia [10,12,14,18,19,21,23–26,28–31,34–40], and six included adolescents with a brain tumour [10,31,36,37,39,40]. Fatigue is a subjective and multifactorial symptom associated with both physical and mental symptoms [10,14,24,25,35,37,38]. Self-reported fatigue was assessed most frequently through the administration of the Fatigue Scale – Adolescent [12,18,19,23,25,26,34,38]; while parent-reported fatigue was most frequently assessed with the Fatigue Scale – Parent [12,18,19,23,25,26]. Adolescents reported anger and distress regarding the limiting effects of fatigue [14,28,37] and the unpredictable nature of onset [10]. In one study, the greater the fatigue perceived by caregivers, the more behavioural and emotional difficulties were demonstrated by adolescents [25].

Five studies indicated a decrease in reported fatigue across treatment times [10,30,31,34,38], and four studies reported that fatigue increased over time [25,26,29,39], although increased fatigue was not always associated with increased distress on a self-report measure [39]. Studies variably indicated that fatigue was [29,33] and was not [11] present prior to treatment administration. The experience of fatigue was significantly associated with dexamethasone treatment [21,23]; however, for a subset of adolescents, fatigue was reported to persist even after the administration of steroids had ceased [38]. Remission was not necessarily associated with decreased fatigue [28]. Four studies reported no gender differences [19,23,29,38], while another study indicated that females reported higher fatigue scores than males [26]. Increased fatigue was reported during hospitalisation [10,14,18,25,26,34,40], with increased number of nighttime wakings being associated with subsequent increase in self-reported fatigue [18]. Changing sleep locations during the night was associated with higher self-reported fatigue [21]. Fatigue was correlated with self-reported sleep quality but not with sleep disturbances measured by actigraphy [12]. Another study similarly reported correlations between self-reported sleep quality and fatigue [21].

Among adolescents treated for a brain tumour who reported fatigue, tumour type/location was specified in only one study (optic glioma) [36]. The majority of adolescents experiencing fatigue were those receiving treatment for leukaemia, and while it is very likely that the treatment included steroids, this component of treatment was reported or assessed specifically in only four studies [12,19,23,38]. Brain tumour patients were receiving treatment, and, while steroids may have been administered, none of the five studies assessed this component of treatment specifically. Of note, no studies were found that examined fatigue in adolescents months or years after treatment for leukaemia or a brain tumour. Strategies used to relieve fatigue included sleeping [10,14,35,36], eating [10,36], self-care (e.g., aromatherapy, hot baths, etc.) [10,14,36], talking to friends and family [10,14,35], medication to improve overall sleep [14,29], and engaging in a purposeful and enjoyable activity [14,35,36].

3.8. Sleep disturbance unspecified

One article reported an unspecified sleep disturbance and included adolescents with brain tumour [49]. Sleep disturbances were assessed via clinical interview during regular evaluation following surgery and were noted to occur in 12% of the study sample.

4. Treating sleep-related difficulties

In order to treat sleep-related difficulties, health care professionals must first be confident in the data on which they base treatment recommendations. Objective measures, such as polysomnography and actigraphy, provide detailed physiological information on sleep but require the use of special equipment, as well as spending the night at a sleep clinic or laboratory. It may be expensive if not completely covered by health insurance. Subjective measures of sleep difficulties are often used in place of or in conjunction with objective measures and while they provide less detailed information on perceived difficulties, they have the benefit of being easily administered and yielding information in a relatively short period of time. A psychometric review of such subjective child- and parent-report sleep measures identified six out of 21 measures that met 'well-established' criteria [50]. Further subjective measure development and validation with objective

measures are needed to ensure that sleep-related problems are correctly identified in a timely manner.

When it comes to addressing sleep problems, the studies included in this systematic review focussed more heavily on symptom identification than intervention or treatment, although a few strategies were reported to be trialled or useful in alleviating the aforementioned sleep problems. Sleep-related difficulties in 'general' (not difficulties related specifically to initiating or maintaining sleep, parasomnias, EDS, etc.) were reportedly alleviated by health-related treatments and pleasurable activities. Health-related treatments included medication [11,19,20,22,35,38,44] and behavioural counselling [11,20,22]. Pleasurable activities included reading [19,20,22,44], playing video games [44], watching television [19,44], a warm bath [19,20,22,44], eating/drinking [19,20,22], sleeping with someone [19,20,22], or having a special blanket or stuffed toy nearby [19,20,22]. Additionally, having a caregiver advocate for a sleep-promoting hospital environment [22] was reported to be helpful. Further study on the effectiveness of different kinds of interventions (e.g., use of a single strategy or a combination of strategies) for various sleep challenges across and among oncology diagnoses appears to be indicated.

5. Discussion

As more study has been undertaken on the specific types of sleep-related disturbances experienced by paediatric oncology patients, increased attention has been paid to the special experiences of adolescents. In this review, the majority of the studies occurred during treatment for leukaemia patients and after treatment for those with a brain tumour. Fatigue appears to have been the most thoroughly studied and best understood symptom of leukaemia treatment, although very few strategies for managing or alleviating it were put forth. For patients with a brain tumour, the majority of studies examined EDS, which appeared to be frequently and often successfully treated with stimulant medications and schedule napping. Sleep-related difficulties and fatigue frequently occurred together, but the directionality of the relationship was unclear, although poor sleep may increase fatigue and fatigue may result in difficulty initiating or experiencing satisfying sleep. Gender differences were not consistently reported across diagnoses for any sleep-related difficulty and study results were sometimes contradictory. While problems related to sleep are common among adolescents undergoing cancer treatment, it is less clear which ones are likely to remit on their own or require an intervention to successfully remediate.

6. Limitations

Sleep-related research among adolescents with cancer has been limited by small sample sizes, samples that include younger children or older adults, inconsistent definition of the age range that comprises adolescence, and sleep measurement using a single item or questionnaire [3]. While many researchers provided separate definitions of daytime sleepiness and fatigue, many others did not, nor was it necessarily clear that adolescents and caregivers differentiated between the two states in their reports. Limitations of the current study include heterogenous age and diagnosis populations, and although an effort was made to tease apart these differences, results may reflect the experiences of younger patients and adolescents with a different oncology diagnosis than leukaemia or a brain tumour. Given that not all studies clearly delineated when patients were or were not receiving steroids but knowing that they likely were if they were undergoing treatment, this review likely underestimates the number of patients receiving steroids and subsequently the effect of steroids on sleep. It should also be noted that the ages of the youth who used the intervention strategies cited in this review were not usually determinable given the ranges across studies and therefore may not be unique to adolescents. In addition, many more interventions for treating paediatric sleep-related disorders exist than were examined in this review, which only examined interventions referenced in identified studies.

7. Conclusion

Adolescents with cancer experience many problems related to sleep, including difficulty initiating sleep, frequent nighttime wakings, disordered breathing, parasomnias, daytime napping, daytime sleepiness/fatigue, and nonspecific disturbances. Difficulties may exist prior to diagnosis, begin with or continue throughout treatment, and continue for years after treatment completion. Given the increase in survival rates of youth diagnosed with leukaemia or brain tumours, symptom management is an essential area of research in order to continue improving quality of life [30,39]. Sleep should be assessed at multiple points in time; such routine screening may assist in the earlier identification or even prevention of sleep-related problems, as well as identify those patients in need of more thorough sleep evaluations, such as polysomnography. For those adolescents treated for a brain tumour, sleep could be assessed prior to surgery or initial administration or chemotherapy or radiation, again at each subsequent treatment administration, at the completion of treatment, and at routine follow-up visits. For patients treated for leukaemia, sleep could be assessed prior to treatment initiation, across the phases of chemotherapy (induction, consolidation, interim maintenance, delayed intensification, and maintenance), during steroid pulses, and after treatment completion at routine follow-up visits. For patients with either diagnosis, it may be important to assess sleep on specific days during a treatment phase to correlate symptoms with treatment side effects, as well as to collect data on symptom variation by time of day and day of the week [24]. As longitudinal studies provide insight into how symptoms develop and change over time, interventions targeting specific sleep-related disturbances can be developed, piloted, refined, and disseminated in order to improve the quality of life of adolescent oncology patients.

8. Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.01.006.

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